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Review

TREAT-AND-EXTEND REGIMENS WITH ANTI-VEGF AGENTS IN RETINAL DISEASES

A Literature Review and Consensus Recommendations

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Purpose: A review of treat-and-extend regimens (TERs) with intravitreal anti–vascular endothelial growth factor agents in retinal diseases.

Methods: There is a lack of consensus on the definition and optimal application of TER in clinical practice. This article describes the supporting evidence and subsequent development of a generic algorithm for TER dosing with anti–vascular endothelial growth factor agents, considering factors such as criteria for extension.

Results: A TER algorithm was developed; TER is defined as an individualized proactive dosing regimen usually initiated by monthly injections until a maximal clinical response is observed (frequently determined by optical coherence tomography), followed by increasing intervals between injections (and evaluations) depending on disease activity. The TER regimen has emerged as an effective approach to tailoring the dosing regimen and for reducing treatment burden (visits and injections) compared with fixed monthly dosing or monthly visits with optical coherence tomography–guided regimens (as-needed or pro re nata). It is also considered a suitable approach in many retinal diseases managed with intravitreal anti–vascular endothelial growth factor therapy, given that all eyes differ in the need for repeat injections.

Conclusion: It is hoped that this practical review and TER algorithm will be of benefit to health care professionals interested in the management of retinal diseases.

RETINA 35:1489–1506, 2015

Three retinal diseases (neovascular age-related macular degeneration [nAMD], diabetic macular edema [DME], and retinal vein occlusion [RVO]) are associated with a major health care burden in Western countries, mainly because of their chronic nature and poor visual outcomes if left untreated. Although the underlying etiology of these diseases is complex, there is now evidence to show that vascular endothelial growth factor (VEGF) plays a key role in their pathogenesis.[1–3] This provides a common rationale for targeting VEGF in retinal diseases. Anti-VEGF agents are effective options, but monthly injections and monthly clinic visits may reduce long-term compliance and increase costs. Monthly approaches have their origins in the standard design of pivotal randomized studies.

To optimize the benefit:risk ratio and cost-effectiveness of anti-VEGF agents, a number of flexible dosing strategies are increasingly being used in clinical practice. These include a variety of as-needed (pro re nata [PRN]) approaches (i.e., regular follow-up with treatment that is determined mostly by recurrent macular fluid on optical coherence tomography [OCT])[4–6] and

treat-and-extend regimens (TERs), which may involve fixed treatment intervals until clinical remission, usually determined by OCT, followed by increasing treatment intervals. A retrospective, observational study of intravitreal ranibizumab in nAMD that examined differences between management in 2007 and 2010 (in 125 eyes) showed that the visual gain was greater (+6.0 vs. +0.7 Early Treatment Diabetic Retinopathy Study letters; $P = 0.0003$) and eyes also received more injections (5.0 vs. 3.8; $P < 0.0001$) in 2010 than in 2007. The temporal change may be because of a number of factors, including the use of alternative strategies, such as TER.[7] However, this study did not directly assess the impact of TER or alternative strategies, and large-scale comparisons in different populations are lacking. There is also wide variation in dosing regimen selection (including TER) in clinical practice[8] and across disease areas.[9] Evaluating the evidence and developing a consensus on the most effective TER protocol would potentially improve regimen selection in clinical practice and enable physicians to understand the rationale for TER, resulting in more considered dosing choices. TER was also regarded as a flexible dosing strategy to reduce retreatment burden in the recently updated EURETINA guidelines.[10] There is also evidence to suggest that intraindividual retreatment intervals are stable but interindividual recurrence intervals are variable.[11,12] This is an ideal basis for individualized treatment plans with TER.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

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Objectives and Methods

The aim of this report is to provide a review and consensus on the best practice approach to the use of TER with anti-VEGF agents (intravitreal ranibizumab, intravitreal bevacizumab, or intravitreal aflibercept) in retinal diseases based on currently available evidence. The review was developed following a roundtable discussion by international retina specialists (consensus panel), which was held in Rome, Italy (26 January 2014), and was also reviewed at a second roundtable meeting held in Tokyo, Japan (01 April, 2014). During the initial meeting, scientific evidence and clinical cases were discussed, followed by the development of an algorithm on the recommended approach to TER; it is envisaged that this algorithm will be useful to ophthalmologists and health care providers with an interest in the long-term management of patients with retinal disease. The scientific evidence has been graded using European guidance (see **Appendix 1, Supplemental Digital Content 1**, http://links.lww.com/IAE/A346).[13]

Scientific Evidence

TER studies. There are 11 published TER studies in more than 1,000 patients with nAMD (Table 1)[14–24]

Table 1. An Overview of "TER" Studies With Anti-VEGF Agents in nAMD

Reference	Design	Treatment	Efficacy Results	Safety Results	Level
Engelbert et al[14]	• Retrospective • FU: 36 months • Type 3 NV/RAP • 10 patients (11 eyes)	3 monthly injections (IVB or IVR) followed by intervals increasing by 2 weeks per visit to a maximum of 10 weeks	• Mean VA: improved from 20/80 (BL) to 20/40 (Month 1); maintained at Year 3 ($P < 0.04$) • Mean OCT CRT: decreased from 320 μm (BL) to 230 μm (Month 1); maintained at 180 μm from Month 3 to Year 3 ($P < 0.02$) • Mean injections (n): 7 (Year 1), 6 (Year 2), 7 (Year 3)	No injection-related complications, such as endophthalmitis or retinal detachment	4
Engelbert et al[15]	• Retrospective • FU: 36 months • Type 1 (subretinal pigment epithelium) NV • 16 patients (18 eyes)	3 monthly injections (IVB or IVR) followed by intervals increasing by 2 weeks per visit to a maximum of 10 weeks	• Median logMAR VA: remained stable from 0.53 (BL) to 0.52 at Year 3 ($P = 0.68$) • Mean injections (n): 12 (Year 2), 20 (Year 3)	15 eyes continued to have SRF; 1 eye developed geographic atrophy; 0 eyes developed submacular hemorrhage (over a 540-month period)	4
Gupta et al[16]	• Retrospective • FU: 24 months • Treatment-naive nAMD • 92 patients (92 eyes)	Monthly injections (IVR) until no fluid on OCT followed by intervals increasing by 2 weeks until exudation recurred	• Mean VA: improved from 20/135 (BL) to 20/83 at Year 2 ($P = 0.002$) • Mean OCT CRT: decreased from 303 μm (BL) to 238 μm at Year 1 ($P < 0.001$) • Mean injections (n): 8.36 (Year 1), 7.45 (Year 2) • Mean extension period: 79.9 days	No adverse ocular or systemic events were reported during FU	4
Shienbaum et al[17]	• Retrospective • FU: 24 months • Treatment-naive nAMD • 73 patients (74 eyes)	Monthly injections (IVB) until no fluid on OCT followed by intervals increasing by 2 weeks until exudation recurred	• Mean VA: improved from 20/230 (BL) to 20/106 at Year 2 ($P < 0.001$) • Mean OCT CRT: decreased from 316 μm to 239 μm at Year 1 ($P < 0.001$) • Mean injections (n): 7.94 (Year 1)	No adverse ocular or systemic events were reported throughout the study	4

(*continued on next page*)

Table 1. (*Continued*)

Reference	Design	Treatment	Efficacy Results	Safety Results	Level
Fung et al[18]	• Randomized • FU: 12 months • Recalcitrant nAMD • 9 patients (9 eyes)	Monthly IVR (0.5 mg or 2.0 mg) followed by TER (up to 8-week intervals) unless exudation recurred	• Main gain in VA (ETDRS letters): 4.1 (2.0 mg) and 3.0 (0.5 mg) at Month 12 • Mean decline in CFT: −40 μm (2.0 mg) and −108 μm (0.5 mg) at Month 6 • Area of leakage (FA): −0.92 mm^2 (2.0 mg) and −1.30 mm^2 (0.5 mg) at Month 6 • Mean injections (n): 6 (2.0 mg) and 5 (0.5 mg)	No adverse events in either group	2
Toalster et al[19]	• Prospective, nonrandomized • FU: 12 months • Treatment-naive nAMD • 45 patients	Monthly IVR until no fluid on OCT followed by intervals increasing by 2 weeks until exudation recurred	• Mean VA: improved from 20/62 (BL) to 20/46 (Month 12) • Mean OCT CRT: improved from 330.9 μm (BL) to 266.3 μm (Month 12) • Mean injections (n): 8	No adverse events reported	3
Abedi et al[20]	• Prospective cohort • FU: 24 months • nAMD (CNV) • 120 patients	Monthly IVB or IVR until no CNV activity (no fluid on OCT, loss of >5 letters, or persistent/recurrent hemorrhage) followed by increasing intervals of 2 weeks (maximum 12)	• Mean change in ETDRS letters was +9.5 (Month 12) and +8.0 (Month 24) • Mean injections/clinic visits (n): 8.6 (Year 1) and 5.6 (Year 2)	Not available	3
Rush et al[21]	• Retrospective • FU: 12 months • nAMD • 230 eyes	3 monthly injections (IVB) until no fluid on OCT followed by intervals increasing by 2 weeks up to 12 weeks; if recurrence, interval reduced by 2 weeks	• Mean VA: improved from 20/55 (BL) to 20/44 (Month 12) ($P < 0.001$) • Mean OCT CMT: improved from 373.1 μm (BL) to 305.5 μm (Month 12) • Mean injections (n): 9.2	Not available	4

Table 1. (*Continued*)

Reference	Design	Treatment	Efficacy Results	Safety Results	Level
Rush et al[22]	• Retrospective • FU: 12 months • nAMD (CNV) • 123 patients	3 monthly injections (IVB) until no fluid on OCT followed by intervals increasing by 2 weeks up to a maximum intervisit interval; if fluid recurrence, BCVA dropped by 2 lines, or leakage on FA, interval reduced by 2 weeks	• Mean change in CNV size: 1.9 mm^2 (BL); 1.66 mm^2 (Month 2); 1.60 mm^2 (Month 6); 1.50 mm^2 (Month 12) • Mean logMAR VA: changed from 0.47 (BL) to 0.33 (Month 12) • Mean injections (n): 9.3	Not available	4
Berg et al[23] (LUCAS)	• Randomized, double-blind • FU: 12 months • Treatment-naive nAMD • 441 patients	IVB or IVR monthly until no fluid on OCT followed by intervals increasing by 2 weeks up to 12 weeks; if recurrence, interval reduced by 2 weeks until macula dry	• Mean ETDRS letters: 69.6 (IVR) and 67.2 (IVB) at Month 12 • Mean change in CRT: −120 μm (IVR) and −112 μm (IVB) at Month 12 • Mean injections (n): 8.0 (IVR) and 8.9 (IVB) (P = 0.001)	APTC-ATEs: 4.5% (IVR) versus 1.4% (IVB) ($P < 0.05$) Nonfatal MI: 2.7% (IVR) versus 0% (IVB) (P = 0.014) Nonfatal stroke: 1.4% (IVR) versus 0.9% (IVB) Injury or procedural complications: 3.2% (IVR) versus 0.5% (IVB) (P = 0.033) One vascular death in each group	2
Rayess et al[24]	• Retrospective • FU: 36 months • Treatment-naive nAMD • 196 patients (212 eyes)	Monthly IVB or IVR until no CNV activity on slit-lamp biomicroscopy/ OCT followed by intervals increasing by 2 weeks; if signs of exudate, interval reduced by 2 weeks	• Mean change in ETDRS letters: +11.6 (Year 1), +10.7 (Year 2), and +13.6 (Year 3) • Mean change in CRT: 351 μm (BL), 285 μm (Year 1), 275 μm (Year 2), and 276 μm (Year 3) (all $P < 0.001$) • Mean injections (n): 7.6 (Year 1), 5.7 (Year 2), and 5.8 (Year 3)	Not available	4

APTC-ATE, Antiplatelet Trialists' Collaboration–defined arterial thromboembolic event; BCVA, best-corrected visual acuity; BL, baseline; CFT, central foveal thickness; CMT, central macular thickness; CNV, choroidal neovascularization; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; FU, follow-up; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; LogMAR, logarithm of the minimum angle of resolution; MI, myocardial infarction; nAMD, neovascular age-related macular degeneration; NV, neovascularization; RAP, retinal angiomatous proliferation; SRF, subretinal fluid; TER, treat-and-extend; VA, visual acuity.

and 3 comparator studies against PRN approaches (Table 2).[25–27] The studies showed an improvement in both visual and anatomical outcomes (central foveal thickness/central retinal thickness/choroidal NV size) using TER, and this approach was associated with greater (and possibly earlier) visual improvements compared with PRN over a period ranging from 6 months to 36 months, with mean injections around 8 in the first year and around 6 to 7 in the second year. There were no major safety concerns with the TER approach, and no eyes developed submacular hemorrhage during an extended follow-up period. The TER approach was similar across studies, with most using a 3-monthly loading scheme until no fluid was seen on OCT followed by 2-week extension intervals up to a maximum of 10 weeks to 12 weeks unless fluid or hemorrhage recurred.

The criteria for treatment extension in each study are summarized in Table 3.[14–21,23,24] In the majority of studies, a dry macula was required before extension (i.e., no fluid on OCT and no persistent or new hemorrhage). Resolution of pigment epithelial detachment was not required before extension; this was particularly relevant in eyes with Type 1 (subretinal pigment epithelium) neovascularization (NV) that will often continue to manifest pigment epithelial detachment after a loading scheme. A number of studies also required a stable disease state before extension and used no change or increase in vision loss or central retinal thickness as markers for treatment change. Fluid recurrence was usually used as a marker for interval shortening. It is expected that fluid recurrence will occur at some stage during an extension phase (making it an important marker); it can, therefore, be used to refine the optimal dosing interval during the follow-up period. At present, there is no optimal approach or guidance for switching from PRN to TER. Changing dosing regimen may be guided by the criteria for extension that have already been described.

There are few studies using TER in macular edema (ME) secondary to RVO or DME (Table 4).[28–30] The consensus panel found the evidence for TER in ME/RVO and DME too scarce to provide general guidance at present. However, based on clinical experience, the proposed TER algorithm will be applicable to ME/RVO and DME. The TER attempts to individualize the dosing regimen and reduce treatment burden (both visits and injections) compared with fixed monthly dosing or monthly visits with OCT-guided regimens, and it can lead to fewer visits (albeit more injections, particularly in the first year of therapy) compared with PRN dosing. These are also considerations for ME/RVO and DME patients. It is also hoped that some of the ongoing TER studies (Table 5) will add further clarity. This will also be valuable in improving the evidence-based treatment guidelines as most of the studies (Tables 1, 2, and 4) are low grade (Level 3–4 evidence) and not registration studies.

Extended follow-up (non-TER) studies. The majority of studies using a TER approach to treatment were performed using intravitreal ranibizumab or bevacizumab. The evidence for intravitreal aflibercept is largely supported by studies that used a 3- to 5-monthly 2 mg dosing scheme followed by dosing every 8 weeks (2q8). Although these were not TER schedules, they are useful in that they illustrate outcomes using an extended dosing regimen in a randomized setting and are registration studies (Level 1 evidence).

In 2 multicenter, active-controlled, randomized studies (VIEW 1 and VIEW 2), 2,419 patients with nAMD and subfoveal choroidal neovascularization were randomized to intravitreal aflibercept 0.5 mg or 2.0 mg monthly or 2 mg every 2 months after 3 monthly loading doses (2q8) or intravitreal ranibizumab 0.5 mg monthly.[31] All intravitreal aflibercept groups were noninferior to monthly intravitreal ranibizumab for vision maintenance at Week 52 (i.e., loss of <15 Early Treatment Diabetic Retinopathy Study letters). Intravitreal aflibercept (any regimen) and monthly intravitreal ranibizumab were equally effective in improving best-corrected visual acuity over a 96-week follow-up, but the intravitreal aflibercept 2q8 group was associated with an average of 5 fewer injections.[32] In addition to it being given at a higher dose, it is possible that the longer dosing regimen with intravitreal aflibercept 2.0 mg compared with intravitreal ranibizumab 0.5 mg observed in the VIEW studies may be linked to differences in binding affinity and a longer intravitreal half-life (approximately 9.0 days vs. 7.1 days, respectively).[33] In the 18-month follow-up of the GALILEO study, visual and anatomical improvements observed with monthly intravitreal aflibercept dosing in patients with ME secondary to central RVO were maintained when the treatment intervals were extended.[34] Intravitreal aflibercept 2q8 has also been shown to be effective in DME patients in two similarly designed, active-controlled, randomized studies (VIVID-DME and VISTA-DME).[35]

Only one large noninferiority study in DME patients (RETAIN) used a treatment approach with extended and reduced follow-up intervals and was considered an "extend-and-treat" study.[36] In RETAIN, patients with DME were randomized to intravitreal ranibizumab with the possibility to modify intervals with laser (Group 1; n = 121) or without laser (Group 2; n = 128) and intravitreal ranibizumab PRN (Group 3; n = 123) over a 24-month follow-up. Both approaches with modified intervals were noninferior to PRN based on mean

Table 2. An Overview of Studies Comparing TER and PRN Dosing Strategies With Anti-VEGF Agents in nAMD

Reference	Design	Treatment	Outcomes	Conclusions	Level
Oubraham et al[25]	• Retrospective, comparator • FU: 12 months • nAMD • 90 patients	• IVR • PRN group (n = 52) and TER group (n = 38)	• Mean gain in VA: +10.8 (TER group) and +2.3 (PRN group) at 1 year (P = 0.036) • Mean injections (n): 7.8 (TER group) and 5.2 (PRN group) ($P < 0.001$) • FU visits (n): 8.5 (TER group) and 8.8 (PRN group)	TER associated with significantly greater VA improvements than PRN; mean injections were higher but visits were comparable	3
Hatz and Pruente[26]	• Retrospective, comparator, switch • FU: 6 months • nAMD • 185 eyes	• IVR • Switch from PRN to TER group (n = 142) • Treatment-naive TER group (n = 43)	• Mean VA improved from: 20/42 (BL) to 20/36 at 6 months (switch group) • Mean injections per month (n) was: 0.47 (PRN) and 0.76 (TER) • Visits per month: 1.10 (PRN) and 0.76 (TER) (P = 0.008)	Switching to TER associated with improvement in VA but with more injections TER was associated with significantly fewer patient visits	3
Calvo et al[27]	• Retrospective, comparator • FU: 36 months • nAMD (CNV) • 60 patients	• IVR • TER group (n = 30) and treat-and-observe group (n = 30)	• Kaplan–Meier survival rates (loss <0.3 units logMAR) were 90.9% (TER) and 89.7% (treat and observe) • VA improved: 42.4% (TER) and 24.1% (treat and observe) • No final VA differences ($P > 0.05$) • Injections (n): 20.31 (TER) and 18.41 (treat and observe)	TER and treat-and-observe regimens showed similar visual outcomes after a 3-year period	3

BL, baseline; CNV, choroidal neovascularization; FU, follow-up; IVR, intravitreal ranibizumab; LogMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; PRN, pro re nata; TER, treat-and-extend; VA, visual acuity.

average best-corrected visual acuity change from baseline to Month 1 through Month 12 (+5.9 and +6.1 vs. +6.2 letters; both $P < 0.0001$). There was an approximately 40% reduction in patient visits in the groups with modified intervals. The design of RETAIN highlights that proactive approaches, such as TER, may be more important to consider in nAMD because it is a more aggressive condition than DME.

Monitoring TER Outcomes Following Anti-VEGF TER

Imaging modalities. It is important to use the most accurate methods to monitor long-term follow-up. The TER studies outlined in Table 3 mainly used spectral-domain OCT or time-domain OCT for measuring fluid as the primary method for treatment extension, and some studies used fluorescein angiography (FA) as a secondary method, particularly if interval shortening was being considered. Leakage on FA, even if not shown on OCT, was one criterion for reverting back to more intensive treatment. We assume that all OCT techniques were performed in accordance with established protocols; however, none of the studies correlated the findings if several OCT techniques were used, and they were not Level 1 type studies.

The reliance on OCT to guide dosing intervals may also be confounded by the data showing that there is often low agreement between spectral-domain OCT and time-domain OCT, particularly for advanced features, such as hard exudates,[37] and also for retinal thickness measurements.[38] A number of studies have reported that spectral-domain OCT may be superior to time-domain OCT for detecting subretinal fluid (SRF)[39,40] and for identifying abnormalities in the absence of fluorescein leakage from choroidal neovascularization.[41] Taken together, these findings indicate that an absence of fluid on spectral-domain OCT or time-domain OCT, resolution of persistent hemorrhage and no new-onset hemorrhage, and no leakage on FA are a benchmark for establishing accurate treatment intervals for TER in nAMD. Fluorescein angiography is also a sensitive technique in detecting leakage associated with ME, making spectral-domain OCT and FA useful for obtaining a comprehensive evaluation in other retinal diseases.[42]

The vitreomacular interface, as imaged with OCT, may also have an influence on treatment intervals in nAMD patients using TER.[43] In one study of 64 nAMD patients, the mean visual acuity in the non-vitreomacular adhesion group (n = 49) was 20/66 compared with 20/67 in the vitreomacular adhesion group (n = 15) at Year 1. The mean central retinal thickness values were 264 μm and 308 μm, respectively. The mean total number of injections was 7.6 (non-vitreomacular adhesion) and 8.7 (vitreomacular adhesion) ($P = 0.028$), and the mean interval between injections was 7.5 weeks versus 6.3 weeks ($P = 0.022$). Applying more sensitive imaging techniques could result in a more accurate prediction of treatment intervals. Other imaging modalities may be considered as optional; however, they are not required for using a TER approach in most patients.

Baseline characteristics. Several studies have examined the relationship between baseline characteristics and long-term outcomes in an attempt to determine predictors of clinical outcomes and to identify eyes that would benefit most from a TER strategy; this is particularly relevant in today's environment because treatment is often started earlier in patients with better baseline visual acuity. One retrospective review involving 230 eyes with nAMD that were treated with intravitreal bevacizumab using TER found that thinner central macular thickness was independently associated with fewer injections.[21]

A more detailed analysis of 185 nAMD patients (210 eyes) treated with anti-VEGF TER therapy over a mean follow-up of 3.5 years (range, 1–6.6 years) showed that the mean visual acuity improved from baseline to final visit in eyes with all neovascular lesion subtypes except Type 3 (intraretina) NV (Type 1 [subretinal pigment epithelium] NV [20/69–20/55]; Type 2 [subretinal pigment epithelium] NV [20/139–20/92]; Type 3 [retinal angiomatous proliferation] NV [20/78–20/83]; and mixed lesions [20/171–20/150]).[44] Most patients received intravitreal ranibizumab only (59%). The rest received a combination of intravitreal ranibizumab and aflibercept (15.7%), intravitreal ranibizumab and bevacizumab (14.3%), all 3 agents (5.7%), intravitreal bevacizumab alone (4.3%), or intravitreal aflibercept alone (1%) but not at the same time. Agents were switched during the course of the study. There were 84 patients (88 eyes) reviewed at 4 years, and the mean visual acuity of these improved from baseline to the 4-year visit in eyes with all neovascular lesion subtypes except Type 3 NV where it was stabilized (Type 1 NV [20/69–20/45]; Type 2 NV [20/139–20/118]; Type 3 NV [20/78–20/79]; and mixed lesions [20/171–20/133]). In the multivariate analysis, a greater number of injections was consistently found to be an independent predictor of better vision at all the time points evaluated (6 months, 1, 2, 3, and 4 years). The mean number of injections per year was 8.8, 7.7, 8.1, and 7.8, respectively. These findings highlight the benefit of TER across all lesion types but show that the best visual outcomes occur in eyes with Type 1 lesions.

Biomarkers. Biomarkers could be a useful adjunct in determining TER strategy in patients who may be nonresponders.[45,46] In one study, a wide range of

proteins was measured using reverse phase microarrays in the preinjection vitreous aspirates from nAMD patients at monthly injection visits before TER. PDGFRβ Y751 and VEGFR2 Y951 were significantly increased in the vitreous of patients who responded with worsening visual acuity (i.e., decrease ≥10 letters) during TER.[45] However, the practical implementation of such assays and techniques in clinical practice may limit the usefulness of their outcomes, except in difficult cases, such as recalcitrant patients or those with a long disease history.

TER Algorithm

Based on the available scientific evidence described, and the experience of the consensus panel, an algorithm on the working definition of TER with anti-VEGF agents in retinal diseases (nAMD, ME/RVO, DME) was devised and is shown in Figure 1. The consensus panel agreed that monthly injections should continue until the following (maximum response) is observed: 1) complete resolution of SRF and intraretinal fluid (IRF) without new retinal hemorrhage or 2) no further reduction of SRF or IRF on OCT for at least 2 consecutive visits in the absence of new retinal hemorrhage. Some panel members would also include 3) no further flattening of serous or vascularized pigment epithelial detachments and 4) no further improvement in visual acuity, in their definition of maximal response. In general, the consensus panel agreed that angiography is not needed in most patients to determine when maximal response has been reached. Once maximal response is achieved, treatment intervals can be extended if there is either a continued absence (preferred) or stabilization of fluid (i.e., no change in IRF or SRF for at least two consecutive injections) on OCT and no new hemorrhage. As small fluctuations in visual acuity are commonly observed in patients seen frequently for intravitreal anti-VEGF injections, the consensus panel felt that visual changes should be evaluated in the context of the clinical examination and OCT findings if they are to be used in guiding the treatment interval. For example, visual acuity loss without signs of choroidal neovascularization activity should not prompt the need for aggressive treatment change, particularly as visual acuity changes could be linked to other factors.

In some eyes with persistent IRF or SRF, a careful review of the OCT and/or additional imaging with angiography may help identify its source. For example, in nAMD, disruption of the outer retinal architecture over fibrovascular tissue or the presence of Type 3 NV (retinal angiomatous proliferation) may be associated with persistent IRF despite monthly treatment. Fluorescein angiography may be useful for detecting lesion growth that may go unnoticed when imaging eyes frequently with OCT. Indocyanine green angiography may help identify polypoidal choroidal vasculopathy that can show resistance to anti-VEGF therapy. In nAMD, ME/RVO, and DME, OCT may show epiretinal membranes or vitreomacular traction that may be related to persistent IRF.

The consensus panel agreed that treatment can be extended by up to 2 weeks at a time if the disease remains stable. The "standard" maximum extension period was considered to be 12 weeks; however, this may also depend on the nature of the disease being treated, for example, shorter for nAMD compared with DME or ME/RVO, monocular patients, eyes at high risk for hemorrhage (e.g., patients taking anticoagulants or those with very large lesions), and the drug being used.

If a patient shows signs of deterioration resulting from disease activity, then the injection interval should be shortened by 1 week to 2 weeks for a minor change (e.g., small recurrences of fluid or small increases in previously stable fluid on OCT, particularly when these changes are accompanied by small degrees of visual loss [<6 letters], or new small, extrafoveal subretinal hemorrhage [even when not accompanied by any vision loss]). If the deterioration is severe (e.g., large recurrences of fluid or large increases in previously stable fluid on OCT, particularly when these changes are accompanied by large degrees of visual loss [≥6 letters], any subfoveal hemorrhage or large extrafoveal macular hemorrhage [even when not accompanied by any vision loss]), then the patient should be reevaluated, and examination of the reasons for deterioration (e.g., FA and/or indocyanine green angiography) may need to be undertaken. In this situation of severe deterioration, reinduction with monthly injection may be considered. Reassessment of treatment interval can be considered once maximal response after a reduced interval is again achieved for two to three consecutive visits. Other longer-term factors to consider following reinjection at maximum interval (and depending on success) include dose change, use of combination therapy, laser, medication change, or treatment suspension.

Further considerations. Although there was some concern regarding the potential development of geographic atrophy, the consensus panel agreed that, in most instances, current evidence favors proactivity with a TER approach rather than risking the negative effects associated with undertreatment. At present, there are insufficient data to determine the association between geographic atrophy and overtreatment with anti-VEGF agents. Studies such as CATT

Table 3. Criteria for Treatment Extension and Interval Shortening in TER Studies

Reference	Criteria for Extension	Fluid Recurrence (Interval Shortening)	Quantitative Assessments Used	
			OCT	Other
Engelbert et al[14]	An absence of IRF and SRF on OCT	6 fluid recurrences occurred in 10 patients during the first 24 months (after establishment of a defined interval)	TD-OCT	Fundoscopy (hemorrhage/tears)
	Resolution of all hemorrhage	During the cumulative observation period of 336 months, a total of 21 fluid recurrences occurred	SD-OCT (fluid/CRT)	
	Resolution of PED not required			
Engelbert et al[15]	An absence of IRF and SRF at foveola	Most eyes (15 of 18 [83%]) continued to manifest extrafoveolar SRF throughout the course of treatment	TD-OCT	FA/ICGA
	Resolution of all hemorrhage		SD-OCT (new hemorrhage/fluid)	Fundoscopy
	Resolution of PEDs and/or extrafoveolar SRF that was judged not to affect VA was not required			Autofluorescence photography (NV/ hemorrhage/GA)
Gupta et al[16]	An absence of IRF or SRF on OCT	7 eyes (7.6%) demonstrated persistent signs of exudation at each visit during FU	TD-OCT Fourier-domain OCT (hemorrhage/fluid)	Slit-lamp biomicroscopy FA (hemorrhage)
Shienbaum et al[17]	An absence of IRF or SRF on OCT	5 eyes (6.8%) demonstrated persistent signs of exudation at each FU visit	TD-OCT Fourier-domain OCT	FA
Fung et al[18]	An absence of IRF or SRF on OCT	71% (n = 5/7) had SRF and 57% (n = 4/7) had IRF at 12 months in the 2.0 mg IVR group 50% (n = 1/2) had SRF and 50% (n = 1/2) had IRF at 12 months in the 0.5 mg IVR group	SD-OCT (fluid)	Fundus examinations FA
Toalster et al[19]	No signs of exudative disease: Vision loss ≥1 line associated with fluid detected by OCT Increase in CRT ≥100 μm New-onset hemorrhage New classic choroidal neovascular membrane Persistent fluid following last injection	Persistent fluid following last injection observed 48 times	SD-OCT (fluid/ hemorrhage)	Fundus examinations FA
Abedi et al[20]	No signs of CNV activity: No drop in VA of >5 letters from the previous monthly visit No persistent or new hemorrhage on dilated fundus examination An absence of IRF or SRF on OCT	Not reported	TD-OCT (fluid)	Fundus examinations

Table 3. (*Continued*)

Reference	Criteria for Extension	Fluid Recurrence (Interval Shortening)	Quantitative Assessments Used	
			OCT	Other
Rush et al[21]	An absence of IRF or SRF on OCT No macular hemorrhage on fundus examination and without growth or leakage of the CNV complex on FA	72 patients (31.3%) could be extended beyond 12 weeks during the 12-month study; however, 51 of those 72 patients developed recurrent exudation beyond the 12-week follow-up interval and required retreatment before the conclusion of the study	SD-OCT (fluid)	Fundus examinations FA/ICGA (NV/ hemorrhage/leakage)
Berg et al[23] (LUCAS)	No signs of active neovascular disease	No fluid on OCT in 47% (IVB) and 65% (IVR) at Year 1 ($P < 0.001$)	TD-OCT SD-OCT Fourier-domain OCT (fluid)	Fundus examinations FA (hemorrhage/ leakage/change in lesion size)
Rayess et al[24]	No signs of CNV activity	Average longest duration of successful extension was 11.4 weeks (Year 1), 13.7 weeks (Year 2), and 13.9 weeks (Year 3)	SD-OCT Fourier-domain OCT (fluid/hemorrhage)	Slit-lamp biomicroscopy (hemorrhage)

CNV, choroidal neovascularization; CRT, central retinal thickness; FA, fluorescein angiography; FU, follow-up; GA, geographic atrophy; ICGA, indocyanine green angiography; IRF, intraretinal fluid; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; NV, neovascularization; OCT, optical coherence tomography; PED, pigment epithelial detachment; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid; TD-OCT, time-domain optical coherence tomography; VA, visual acuity.

Table 4. An Overview of TER Studies With Anti-VEGF Agents in ME Secondary to RVO

Reference	Design	Treatment	Efficacy Results	Safety Results	Level
Brady et al[28]	• Retrospective • FU: 6 months • Treatment-naive CRVO • 25 patients	TER approach with IVB or IVR	• Mean VA: improved from 20/200 + 1 (BL) to 20/80 • Mean CMT: improved from 652 μm (BL) to 422 μm	Not available	4
Campochiaro et al[29]	• Prospective • FU: 49 months • CRVO or BRVO • 66 patients	IVR Monthly visits (Year 1) 3-monthly visits (Year 2) (extend-and-treat regimen)	• Edema resolution (no intraretinal fluid for ≥6 months after last injection) in 50% (n = 17/34) (BRVO) and 44% (n = 14/32) (CRVO) • Patients with resolved CRVO had greater improvement in BCVA (25.2 vs. 4.3 letters; $P = 0.002$) than unresolved CRVO	Two patients had events probably related to vitreous traction	3
Rush et al[30]	• Retrospective • FU: 12 months • BRVO–ME • 52 patients	TER approach with IVB	• Mean logMAR VA: improved from 0.54 to 0.24 ($P < 0.001$) • Mean CMT: improved from 490.0 μm (BL) to 246.0 μm ($P < 0.001$) • Mean injections (n): 8.2	No systemic adverse events	4

BCVA, best-correct visual acuity; BL, baseline; BRVO, branch retinal vein occlusion; CMT, central macular thickness; CRVO, central retinal vein occlusion; FU, follow-up; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; logMAR, logarithm of the minimum angle of resolution; ME, macular edema; TER, treat-and-extend; RVO, retinal vein occlusion; VA, visual acuity.

Table 5. Key Ongoing Studies Including Those Using TER (Status: October 2014)

Title	Disease	Main Sponsor(s)	Primary Drugs	Study Identifier(s)	Objective(s)	Primary Endpoint	Primary Endpoints Reported
A Phase IIIb, multicenter, randomized study of the safety, tolerability and efficacy of IVR 0.5 mg given monthly compared to TER	AMD	Genentech	Ranibizumab	NCT01748292 T-REX	To maintain an exudation-free macula with the fewest number of office visits, tests, and injections	Mean change in ETDRS visual acuity from Day 0 up to 24 months	January 01, 2015
A Phase IIIb, 12-month, randomized, visual acuity, assessor-masked, multicenter study of the efficacy and safety of IVR 0.5 mg given monthly compared to TER	AMD	Novartis	Ranibizumab	NCT01948830 TREND	To evaluate the efficacy and safety of IVR TER versus monthly regimens	To demonstrate that the TER is noninferior to the monthly regimen as assessed by the change in BCVA from baseline to Month 12	October 01, 2015
A 12-month, Phase IV, randomized, open-label, multicenter study to compare the efficacy of IVR 0.5 mg PRN versus IVT-AFL 2 mg bimonthly	AMD	Novartis	Ranibizumab Aflibercept	NCT01958918 SALT	To compare IVR PRN (BCVA loss and/or SD-OCT disease activity–guided retreatment) versus IVT-AFL bimonthly	To compare IVR 0.5 mg PRN versus IVT-AFL 2 mg bimonthly on SD-OCT CRT stability (as measured by mean CRT fluctuations between Months 3 and 6)	July 01, 2016

Table 5. (*Continued*)

Title	Disease	Main Sponsor(s)	Primary Drugs	Study Identifier(s)	Objective(s)	Primary Endpoint	Primary Endpoints Reported
Phase IV study	AMD	Novartis	Ranibizumab	NCT02103738 CAN-TREAT	To compare 2 IVR treatment regimens (standard of care and TER); to achieve and maintain a maximum visual function benefit; to evaluate AMD disease (based on recurrence of disease instability)—for making treatment decisions	Mean change in BCVA from baseline to Month 12	May 01, 2017
OCT-guided TER therapy using IVT-AFL	AMD	Regeneron	Aflibercept	NCT01773954 ATLAS	To evaluate the visual outcomes and number of injections required during OCT-guided TER with IVT-AFL	Mean change in BCVA (ETDRS) letter score	November 30, 2014
Treat-and-extend therapy using IVT-AFL for previously treated patients exiting the wet AMD extension study (0910)	AMD	ISS	Aflibercept	NCT01961414 RANGE	To evaluate a TER (increasing the time between visits when the disease is stable and not getting worse) of IVT-AFL 2.0 mg	Portion of patients who maintain vision (loss of $\leq$5 letters ETDRS BCVA) from baseline to 12 months	March 31, 2015
A Phase I/II, open-label, multicenter, randomized study of the safety, tolerability, and efficacy of IVR 0.3 mg given monthly compared to TER protocol	DME	ISS	Ranibizumab Laser photocoagulation	NCT01934556 TREX DME	To compare the visual outcomes between patients who are treated with IVR as monthly or TER	Mean change in vision (ETDRS) at 24 months	November 01, 2016

(*continued on next page*)

Table 5. (*Continued*)

Title	Disease	Main Sponsor(s)	Primary Drugs	Study Identifier(s)	Objective(s)	Primary Endpoint	Primary Endpoints Reported
A comparison of IVR and IVT-AFL for the development of GA in AMD patients	AMD	Novartis	Aflibercept Ranibizumab	NCT02130024 RIVAL	To assess the development of GA with either ranibizumab or aflibercept in patients with AMD	Proportion of patients with newly developed GA as assessed by multimodal imaging	December 01, 2017

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; ISS, Investigator-sponsored study; IVR, intravitreal ranibizumab; IVT-AFL, intravitreal aflibercept; OCT, optical coherence tomography; PRN, pro re nata; SD-OCT, spectral-domain optical coherence tomography; TER, treat-and-extend.

(Comparison of Age-related macular degeneration Treatments Trials) and IVAN (a randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation) used suboptimal imaging,[4,5] making any distinction between treatment effects and natural disease course on geographic atrophy rates difficult. Further study is needed to determine if certain eyes at very high risk of geographic atrophy (such as those with a very thin choroid, reticular pseudodrusen, and possibly those presenting with Type 3 NV [retinal angiomatous proliferation])[47–51] might be more safely managed with a PRN regimen to reduce the risk of geographic atrophy progression. A new study in 91 patients (94 eyes) showed that treatment-naive age-related macular degeneration patients with Type 1 NV were significantly ($P < 0.001$) less likely to develop geographic atrophy after anti-VEGF treatment compared with other subtypes. The majority of patients received ranibizumab (63.8%), bevacizumab (9.6%), ranibizumab plus bevacizumab (5.3%), ranibizumab plus intravitreal aflibercept (18.1%), or all 3 agents (3.2%); the mean follow-up was 28.5 months and the mean number of injections was 17.4.[48]

The consensus panel also suggested that a TER approach may reduce the risk of intraocular pressure (IOP) elevation compared with monthly (but not PRN) dosing; prevalence of sustained IOP was significantly higher when the intervals between injections were <8 weeks compared with ≥ 8 weeks (17.6% vs. 6%, $P = 0.009$).[52] In a 6-month retrospective study of 328 patients (449 eyes) with nAMD treated with intravitreal ranibizumab or bevacizumab, 32 eyes (7.1%) developed sustained IOP (defined as absolute IOP >25 mmHg, increase above baseline >10 mmHg, or IOP of >21 mmHg and increase of >5 mmHg) that was significantly linked to the number of injections (hazard ratio, 1.085; 95% confidence interval, 1.06–1.11).[53] Physicians may also need to consider the differences between transient postinjection IOP spikes related to injection volume and needle gauge and sustained IOP elevation occurring over the course of long-term treatment, and risk factors such as preexisting glaucoma, ocular hypertension, and rapid injection technique.[54–56] Another study in 22 patients (44 eyes) with nAMD showed no significant difference in retinal nerve fiber layer thickness between eyes treated with intravitreal ranibizumab using TER and the untreated fellow eye. Furthermore, there was no difference in retinal nerve fiber layer thickness in eyes treated with fewer or more than five injections.[57]

At present, there are few studies to determine patient-centered preferences for TER, including improvements in compliance with less frequent visits and any

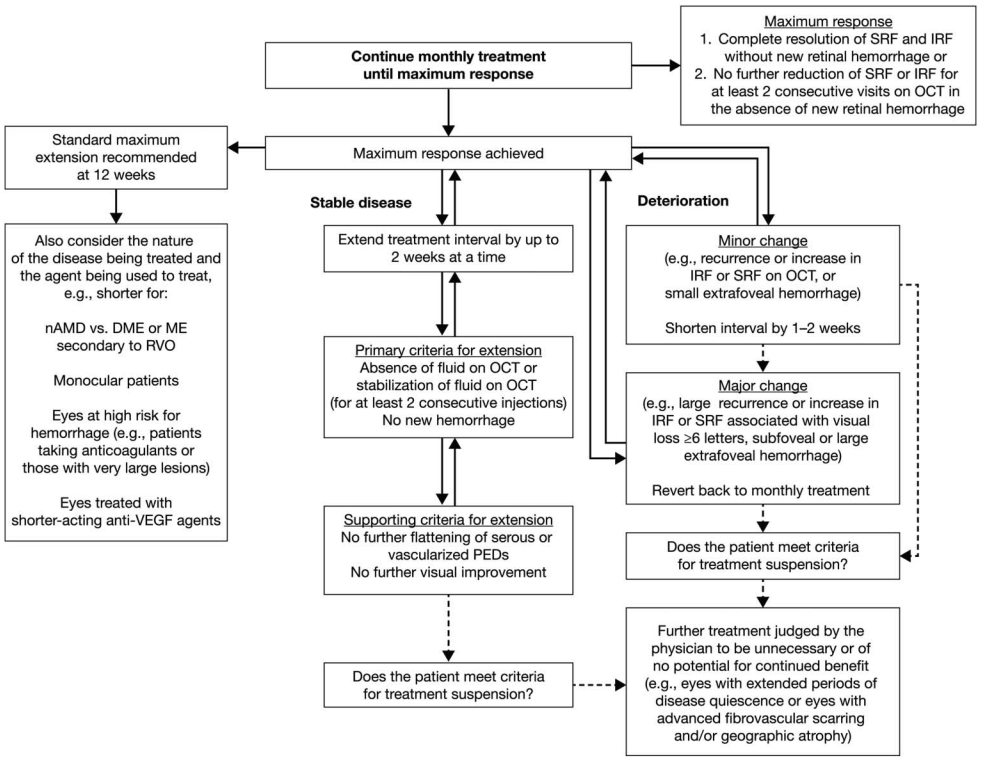

Fig. 1. Algorithm showing the working definition of TER. PED, pigment epithelial detachment.

tolerance to fluid during optimization of dosing regimen, to make any strong conclusions regarding patient choice. Surveys of Medicare beneficiaries (284,380 claims [2006–2008] and 459,237 claims [2014 update]) show that the frequency of anti-VEGF injections remains lower than that recommended in clinical studies, with high discontinuation rates (71% within 24 months).[58,59] One 4-year longitudinal study that investigated the pattern of discontinuation in 555 patients (600 eyes) with age-related macular degeneration treated with a variable intravitreal ranibizumab dosing regimen from 2007 to 2011 found that 68% (408 eyes) discontinued: 28% because of lack of response, 11% failure to follow-up, 9% death, and 20% disease inactivity. Treatment was resumed for 18% in this last group, suggesting that eyes with inactivity should still be monitored.[60]

It is possible that using a longer interval for treatment follow-up could address some of the issues observed in observational settings. In the long-term study, Mrejen et al[44] reported that the retention rate was 64% over a mean follow-up of 3.6 years in 231 nAMD patients treated with anti-VEGF agents using a TER approach. These findings indicate that a TER may improve retention rates in the long term, but this has yet to be investigated in large-scale observational cohorts. About the issue of tolerance to fluid, some eyes with Type 1 NV managed with TER can have

Table 6. Advantages and Disadvantages of TER Over PRN

Advantages	Disadvantages
Fewer recurrences	Overtreatment/may inject eye with a dry retina and achieve no VA change
Better long-term vision outcomes	Does not identify the patient who may remain stable without treatment (particularly for DME and RVO)
More likely to keep retina dry	Potentially greater risk of geographical atrophy
Less patient visits	Increased chance of getting an adverse event
More proactive	Limited evidence
Guarantee of some injections	No stop criteria in DME and RVO
Reduced risk of hemorrhage	
Adherence, logistics, costs	
Better disease control/stability	
Individualized to patient	
More predictable injection workload	

DME, diabetic macular edema; PRN, pro re nata; RVO, retinal vein occlusion; TER, treat-and-extend; VA, visual acuity.

good long-term visual outcomes with anti-VEGF therapy despite some persistent SRF throughout the course of treatment.[15,61]

From a cost perspective, the TER approach could be associated with cost benefits compared with monthly regimens. As an early indication, Gupta et al[16] reported that the mean direct costs (per patient) of the intravitreal ranibizumab TER used in their study were US $16,114.52 (Year 1) and US $13,971.44 (Years 1–2), respectively; this was lower than that observed over a 1-year period in MARINA/ANCHOR (US $28,314.16). However, these cost estimates are now outdated, and any cost analyses would benefit from inclusion of a wider cohort.

It must also be noted that a physician may consider a number of reasons for not choosing TER, including patient choice, preference for minimal number of injections, particularly in bilateral eye disease, severe glaucoma where repeat pressure spikes may be a concern, previous endophthalmitis, or other adverse reactions.

Conclusion

The aim of this consensus article is to consider the best-practice approach to the use of a TER regimen with anti-VEGF agents (intravitreal ranibizumab, bevacizumab, and aflibercept) based on available scientific evidence and clinical experience. There are a number of limitations associated with this nonsystematic review and consensus. First, the published studies of anti-VEGF TER are low-grade, nonregistration studies, which are not Level 1 type evidence. The studies would therefore be subject to issues inherent with the retrospective design of many of them. Other issues include selection bias (including the exclusion of noncompliant patients); the use of different imaging techniques, with no correlation between OCT modalities used; and Type II errors, arising from the lack of monthly regimens for comparison of efficacy and safety outcomes. The consensus also represents the view of clinical experts in the field and is subject to bias and limitations associated with health care systems in different countries. The international, observational AURA (a retrospective non-interventional study to assess the effectiveness of existing Anti-vascular endothelial growth factor treatment Regimens in patients with wet Age-related macular degeneration) study found that patients are undertreated with ranibizumab in real-life settings; this may be because of the difficulty of using monthly regimens in clinical practices.[62] The TER algorithm represents a useful guide that may lead to an improvement in the minimum number of injections being used and may help address some of these issues. The TER is practical and realistic in that it does not overemphasize the need to achieve complete absence of fluid. It must be noted, however, that this is a general guide and may not be applicable to unusual cases in which physician expertise is required.

In summary, TER is considered a suitable approach in a variety of retinal diseases—given that all eyes differ in their need for injections (Table 6). A generic TER approach could be used in most diseases, based on achievement of a maximum (preferably optimal) response followed by 1-week to 2-week extension intervals that are guided by anatomical measures, with visual changes as a secondary guide for interval extension. The maximum extension period may depend on the anti-VEGF agent used. If disease activity increases, the injection period should be shortened by 2 weeks, with complete reassessment for a major change (such as hemorrhage). There are also a number of well-designed, randomized studies that are ongoing that will help further refine the optimal approach to TER when these data become available.

Key words: treat-and-extend, anti-VEGF agents, ranibizumab, bevacizumab, aflibercept, age-related macular degeneration, diabetic macular edema, retinal vein occlusion, algorithm.

Acknowledgments

Editorial assistance was provided by S. Phillips, PhD, PAREXEL, who was funded by Bayer Pharma AG.

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